entered in the present application by Applicant's Amendment of November 19, 2003, and (2) the Examiner subsequently held telephonic conversations with Applicant's undersigned (new) representative as was memorialized in Applicant's supplemental response of January 20, 2004.

The Office Action of March 23, 2004, is mis-addressed to Applicant's former attorneys. Please address further communications on this application to Applicant's undersigned representative. (If the change in power of attorney is somehow not within the file and/or is found insufficient, then please mail the former attorneys while **also** copying the undersigned as provided for in the MPEP).

2. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-17 and 103-116 were rejected under 35 U.S.C. §112, first paragraph.

2.1 New Rejections -- Under 35 U.S.C. §112, First Paragraph -- in a Final Office Action

The rejection of claims 1-17 and 103-116 under 35 U.S.C. §112, first paragraph is newly made. It is **not** necessitated by Applicant's amendment to the claims, nor by any argument(s) newly made by Applicant. Accordingly, the **final** status of the present Office Action is improper, and is deemed premature under MPEP §706/07(c): "Under present practice, second or any subsequent action on the merits shall be final, **except** where the examiner introduces a new ground of rejection not necessitated by the amendment of the application by applicant..." MPEP §706.07(a) (boldface added).

The Examiner is called upon to withdraw the **final** rejection as premature under the procedure of MPEP §706/07(d).

2.2 Substantive Argument to the [New] Rejections Under 35 U.S.C.

§112, First Paragraph

The Examiner finds that Applicant's specification lacks description, and working examples, as to how to successfully practice without undue experimentation Applicant's claimed method.

In fact Applicant's invention of a method of labeling DNA with a magnetic label (ferrofluid) lacks such detail as the Examiner seems to desire because it is so simple. Perhaps Applicant's simple ionic labeling method seems to lack detail when compared to more complex labeling methods of the prior art, but all the user need do is to add the sample to a tube, add the ferrofluid, pull down the composite and wash several times, and the [labeling portion of] Applicant's method is then complete!

Dealing with the Examiner's specific comments; first, the production and manipulation of a magnetic field is so common that it is within the ability of a routineer in the art, and as such a detailed description of such is not needed in the application. The use of an electromagnet for producing and manipulating magnetic field is well understood.

Second, a Giant Magnetoresistive (GMR) effect sensor is a tool for reading the magnetic signal of samples, and can be purchased off the shelf both at time of application filing and now to read a DNA sample. Applicant is not patenting GMR sensors, and deems additional detail (not within the specification) for the GMR sensor and the GMR sensor technology unnecessary (under 35 U.S.C. §112, First Paragraph).

The Examiner objects to the "Hypothetical Ferromagnetic material", the hysteresis of which magnetic material is shown within Figure 2, and which material is described at specification page 15 lines 15-20. The "Hypothetical Ferromagnetic material" is a mere example to (1) introduce the reader to the concept of hysteresis, and to (2) define terms by example. In Figure 3 and associated text Applicant teaches his invention, in detail, with

the use of specific known ferromagnetic materials.

Namely, Applicant's present invention includes methods and systems to permit assessment of the **ratios** of magnetization parameters. For example, the ratio of remnant magnetization to the saturation magnetization is known as the "remnant squareness" of the hysteresis loop. The slope of the M-H curve when the hysteresis loop crosses zero magnetization (i.e., at the coercive force designated 12 in Figure 2) is also a characteristic of the particular magnetic material.

Another parameter known as "loop squareness" approaches 1 as the hysteresis curve at this point becomes increasingly vertical.

These and other parameters **derived from the hysteresis curve** may be especially useful in differentiating magnetic labels, as the measured numerical value of a **ratio** of measurements (or a rate of change of magnetization) can be made to be less dependent on the concentration of label in the sample being measured.

In Figure 3 is a graph illustrating magnetization as a function of applied field intensity for two different materials. This graph shows the upper left quadrant of the hysteresis curve for neodymium iron boron 13, and also for samarium cobalt 14. It can be seen from examination of this Figure 3 that the neodymium iron boron material has (1) a higher saturation magnetization, (2) a lower coercive force, and (3) a steeper slope at zero magnetization. At least these features may be used to distinguish the presence of magnetic labels made from different materials.

Embodiments of the present invention measure the magnetization of a selected sample material as a function of applied magnetic field strength. From these measurements, aspects of the hysteresis loop exhibited by the sample are determined. Three types of instruments frequently used to characterize the magnetic properties in materials are (1) the 60-Hz M-H looper, (2) the toroidal B-H looper, and (3) the vibrating

sample magnetometer (VSM). Any of these instruments are, and were at time of application filing, commercially available (replete with instructions for use). Still other instruments, or other comparable equipment or systems, can be used in accordance with Applicant's invention to measure the magnetic properties of magnetic labels.

Therefore, in Applicant's claimed invention a sample containing a magnetic label of a first kind is distinguishable, and is distinguished, from a sample containing a magnetic label of a second kind. Typically, and as is particularly illustrated by Figure 3, the different labels will have different chemical composition. For example, two ferromagnetic labels can comprise (1) two different iron alloys, or, alternatively, (2) an iron based label and a rare earth element based label. Samples containing these labels will exhibit hysteresis loops having different shapes, and the labels are thus distinguishable under an applied external magnetic field by analysis of the magnetization of each. Notably, mixtures of two different labels are also detectable because the sample will exhibit a hysteresis loop having characteristics that are intermediate between the loops exhibited by the two labels individually.

The present invention still further includes methods and systems for detecting and characterizing magnetic labels that are attached to a biomolecule disposed on a support. Because magnetic labels attached to a biomolecule generate a quantifiable magnetic field (as explained in Applicant's specification, and yet again above), both the presence and the location of biomolecule on the support can be determined.

For example, in one preferred embodiment of Applicant's invention described in the specification at page 27 and again at page 35, when a support having a biomolecule attached to a magnetic label is juxtaposed with a magnetic sensor and moved past the magnetic sensor, then the magnetic field of the attached

magnetic markers variably permeate the sensor and thereby cause the sensor to generate a detection signal. For label characterization, (1) an external magnetic field is applied, and (2) sample magnetization is measured at a plurality of applied field strengths, all as Applicant teaches and describes. When detecting the presence of label, the support is preferably closely juxtaposed with the sensor and, still more preferably, the substrate is distanced from the sensor -- in the way of the described example only -- by only a few microns or less, thereby so as to improve the sensitivity of detection.

In still other described embodiments of Applicant's invention, the support and the sensor may be integrated. The sensor (1) is electrically connected to a signal processor that receives the detection signal and (2) generates a signal representative of the amount of magnetic label present.

Likewise as the Examiner apparently does not recognize the routine nature of the quantification, and the comparison, of magnetic fields produced by, inter alia, ferrofluids so as to thus serve as indication of the (1) presence and (2) abundance of specific ferrofluids, the Examiner questions the use of the term "RMU". "RMU", standing for "Relative Magnetic Units", was used because the common way to express fluorescent intensities is in "RLU", or "Relative Light Units". In both cases absolute measurements are not required. In both cases a known amount of sample is used to calibrate the system. With fluorescent emissions the amount of cell or DNA is measured so as to develop a standard where a certain amount of light represents a certain amount of DNA. Applicant's invention functions equivalently, and would be recognized to so function by a routineer in the art. Namely, in the case of Applicant's system a magnetic signal represents the amount of DNA. However, to give absolute magnetic measurements would be both unsound, and unnecessary. Remember, Applicant's invention functions to detect magnetic labels by

deducing the **ratio** of the magnetization signals (the hysteresis curves) induced by an applied magnetic field. The measurements Applicant actually took in an operative reduction to practice of his system and method were both robust and linear, and are shown in Figure 5 and Figure 6 and described in the associated text.

The Examiner finds an issue as to whether "the rest of the recited magnetic features would behave similarly". Applicant agrees that his data presented would not yield the full hysteresis loop. But such is **unnecessary**! One **can** get magnetic saturation from Applicant's shown measurements. Applicant has not manipulated the magnetic field in producing his shown data set. In Figure 4 the data presented is the result of linear scan that yielded each of (1) the presence and (2) the location and (3) the quantity of magnetic DNA. Figures 5 and 6 are still better examples of measuring quantity.

Next, Applicant's invention still further transcends the mere detection of ferrofluid complexes bound to a surface with a magnetic sensor -- important as that may be. Applicant further contemplates, and teaches, multiplexing of his detections/measurements, and of the ferromagnetic species detected/measured.

3. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-17 and 103-116 were rejected under 35 U.S.C. §112, second paragraph (although only claim 1 is commented upon, and claim 116 is also an independent claim).

The term "as well as" in claim 1 is amended to --and--; and the term "some one or more" is amended to --any--.

Claim 12 is amended for grammar; claim 113 is amended for spelling; and claim 116 is amended for punctuation. (Claim 15 is amended for clarity in response to the Examiner's rejection under 35 U.S.C. §103; see below.)

4. Rejections Under 35 U.S.C. §102

The Examiner rejects claims 1-2, 5, 8, 9, 16-17 and 112-116 under 35 U.S.C. §102 over the reference art of Rohr.

Rohr uses "magnetic response" in determining the force or influence on the magnetic label. Applicant finds neither the word "signal" nor "location" within Rohr. [Applicant claims "...measuring and characterizing a magnetic **signal**... [so as to] identify any of the presence, **location**, orientation.... (Claim 1) (boldface added)]

Rohr is measuring force, and, at best, thus indirectly magnetic signal -- but that is a stretch. Rohr neither teaches nor suggests "determining one or more magnetic characteristics [of the signal]" (claim 1). If the Examiner thinks that the process of contacting a the test sample with an immobilized probe is anticipated then he is correct. That is the a common way of doing a bioassay! However, it is (1) the resulting signal and (2) how it is measured that is the subject of Applicant's claimed invention.

The Examiner, possibly in hindsight of Applicant's invention, is reading more into Rohr then is there. For example, the Examiner posits as an example the use of particles of neodymium-iron-boron -- a particle the magnetic characteristics of which are known -- by Rohr. But as you read the example of Rohr in some detail you will see that neodymium-iron-boron is being used as the permanent magnet that Rohr uses in his force measurement -- **not** as a label! Rohr is using as a label a common magnetic iron compound like Fe2O3!

Rohr could have simply placed his sample on a scale and measured the additional weight or the change in weight when a magnetic force vector is used to add or subtract the weight.

A basic difference between the teaching of Rohr and the claimed invention of Applicant is that Applicant can read a sample and a produced electrical signal that is the **direct** result

of the applied magnetic field. Applicant reads the magnetics of the sample **directly**, and not as a force on some mirror that deflects a light beam, nor as a balance beam torque reading. This difference is so basic that one schooled in the art would **not** jump from Rohr to Applicant's invention. Rohr neither teaches nor suggests Applicant's claimed invention of "determining one or more magnetic characteristics [of the magnetic signal of a target probe complex]" (claim 1).

5. Rejections Under 35 U.S.C. §103

5.1 Rejections Under 35 U.S.C. §103 over Rohr in View of Pirrung, et al.

Claims 3, 4, 6, 7, 10-11, 12-14 and 110-111 were rejected under 35 U.S.C. §103 over the reference art of Rohr in view of the reference art of Pirrung, et al.

Applicant cites the Pirrung method and patent in his specification as an example.

Pirrung, et al., do nothing to overcome the deficiencies of Rohr to teach or suggest **direct** reading of **magnetic properties**. Applicant fails to see how any combination of Rohr and Pirrung, et al., so as to produce an array of magnetic balances or strain gauges, and/or cantilever mirrors, suggests Applicant's claimed array. Rohr is making his magnetic force measurements in 3-D on in the 2-D plane of an array. How do you do an x-y scan using a strain gauges or a cantilever, or how do you build an array out of this technology? Applicant's claimed array (of claim 3) is **not** obvious under 35 U.S.C. §103.

Meanwhile, Pirrung, et al., teach how to build array on glass like surface using technology from the chip-making field. Pirrung, et al. do **not** show how to measure a signal on the surface of their arrays, **nor** how to build or include a sensor below, beside or above any sample. The arrays in Pirrung, et al., must be of a specific size or larger. Applicant is using an

array as a platform or stage for his sample, which is to be put on, below, beside or above the sensor array. It is irrelevant whether this array is, or could be, built using Pirrung, et al., technology or not.

5.2 Rejections Under 35 U.S.C. §103 over Rohr in View of Moeremans, et al.

Claim 15 was rejected under 35 U.S.C. §103 over the reference art of Rohr in view of the reference art of Moeremans, et al.

In claim 15 Applicant claims such contacting of his "target molecule of molecular complex with a non-magnetic colloid" (claim 15) as will result, in Applicant's system, with said non-magnetic colloid being a **blocking** buffer. Claim 15 is amended so as to make this clearer.

In Moeremans, et al., such a non-magnetic colloid it is used in a step in a colorimetric reaction where it's purpose is to react with a added chemical to produce a change in color. Yes, the non-magnetic colloid of Moeremans, et al., binds with the DNA. Indeed, the DNA it binds with is what Moeremans, et al., is doing so as to develop a color so that the DNA may be seen.

Thus Applicant is using, and claims to use, his colloid **oppositely** from Moeremans, and so as to **block** a magnetic signal which would otherwise be seen from the DNA bound to the solid surface. By such blocking Applicant sees only that DNA that was reacted. Moreover, Applicant measures his signal in one step; not the several steps as required by Moeremans.

6. Summary

The present amendment and remarks have overcome and discussed each of the bases for the rejections presented in the Office Action. No new subject matter has been introduced by the present amendment.

In consideration of the preceding amendment and accompanying remarks, the present application is deemed in condition for allowance. The timely action of the Examiner to that end is earnestly solicited.

Applicant's undersigned attorney is at the Examiner's disposal should the Examiner wish to discuss any matter which might expedite prosecution of this case.

Sincerely yours,

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